REMARKS

Currently, claims 6, 13, 16, and 28-38 are pending in the present application, including independent claims 6 and 33. Independent claim 6, for instance, is directed to a pharmaceutical composition "consisting essentially" of 5-[[4-[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiazolidine-2,4-dione or a pharmaceutically acceptable salt thereof, and pharmaceutically acceptable excipients. The excipients consist essentially of anhydrous lactose, microcrystalline cellulose, magnesium stearate, and talc. Likewise, independent claim 33 is directed to a tablet formed by direct compression of a composition that consists essentially of 5-[[4-[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiazolidine-2,4-dione or a pharmaceutically acceptable salt thereof, and pharmaceutically acceptable excipients. The excipients consist essentially of between 100 and 400,000 parts by weight of anhydrous lactose and between 111 and 10,000 parts by weight of microcrystalline cellulose, expressed in parts by weight per 100 parts of 5-[[4-[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl] thiazolidine-2,4-dione or one of its pharmaceutically acceptable salts.[1]

In the Office Action, independent claim 6 was rejected under *35 U.S.C. § 103(a)* over WO 97/41097 to Lohray, et al. in view of U.S. Patent Nos. 6,866,867 to Staniforth et al. and 4,280,997 to Van Leverink. Lohray, et al. is directed to an azolidinedione

[1] Example 2 of the present application includes 18% active and 20% microcrystalline cellulose. Thus, microcrystalline cellulose constitutes *111 parts by weight* (100/18 x 20) per 100 parts of 5-[[4-[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl] thiazolidine-2,4-dione, potassium salt. This corresponds to the lower limit of new independent claim 33. Accordingly, no new matter has been added. *See M.P.E.P. § 2163.05(III)*; *In re Wertheim*, 541 F.2d 257 (CCPA 1976).

derivative and its use in the treatment of diabetes and related diseases. The only excipients mentioned by Lohray, et al. are found on p. 35. More specifically, Lohray, et al. refers to the following compositions (a) and (b):

(a)

	Amount (g)	Parts per hundred
Active	10	-
Lactose	110	1100
Corn Starch	35	350
Carboxymethyl cellulose	44	440
Magnesium Stearate	1	10

(b)

	Amount (g)	Parts per hundred
Active	10	-
Calcium phosphate	90	900
Lactose	50	500
Corn Starch	45	450
Polyvinyl pyrrolidone	3.5	35
Magnesium Stearate	1.5	15

As noted above and correctly acknowledged by the Examiner, Lohray et al. completely fails to disclose the use of the claimed *anhydrous lactose* and *microcrystalline cellulose* low water content excipients. Nevertheless, the Office Action cites Van Leverink and Staniforth et al. in an attempt to cure the defects of Lohray et al. Namely, the Office Action cites Van Leverink for the teaching of anhydrous lactose and Staniforth et al. for the teaching of microcrystalline cellulose, and argues that it would have been obvious to substitute "anhydrous" lactose for the lactose component of Lohray, et al. and to also substitute "microcrystalline cellulose" for the carboxymethyl cellulose component of Lohray, et al.

Even if combined in this manner, however, Applicants respectfully submit that the references still fail to disclose certain aspects of independent claim 6. Both of the compositions (a) and (b) of Lohray, et al., for example, require the use of a significant portion of "corn starch" (350 or 450 parts per hundred). Independent claim 6, however, is directed to a pharmaceutical composition "*consisting essentially*" of 5-[[4-[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiazolidine-2,4-dione or a pharmaceutically acceptable salt thereof, anhydrous lactose, microcrystalline cellulose, magnesium stearate, and talc.[2] Claim 6 thus expressly excludes "corn starch" as an excipient as it may have a material affect on the stability of the active ingredient in the presence of and in contact with water. This is supported by the data presented in Applicants' previous response of February 3, 2005, which is reproduced below for the Examiner's convenience.

Formulation	1		2		3	
Content of formulation (mg/tablet)	Active Ingredient	10.96 mg	Active Ingredient	10.96 mg	Active Ingredient	10.96 mg
	Microcrystalline cellulose	80 mg	Maize starch	35 mg	Maize starch	45 mg
	Lactose DCL 21	289 mg	Lactose	110 mg	Lactose	50 mg
	Magnesium stearate	2 mg	Carboxymethyl cellulose	44 mg	Calcium phosphate	90 mg
	Talc	18 mg	Magnesium stearate	1 mg	Polyvinyl pyrrolidone (Kollidon K 30)	3.5 mg
					Magnesium stearate	1.5 mg
Description of formulations	Corresponds to example 1 in the present application with respect to content, except for a lower content of active ingredient. The tablets were prepared by direct compression.		Corresponds to example (a), page 35 in WO 97/41097. Tablets were prepared by wet granulation.		Corresponds to example (b), page 35 in WO 97/41097. Tablets were prepared by wet granulation.	

[2] The transitional phrase "consisting essentially of" limits the scope of the claim to the specified ingredients "and those that do not materially affect the basic and novel characteristic(s)" of the claimed invention. *In re Herz*, 537 F.2d 549, 551-52 (CCPA 1976).

* Active ingredient is 5-[[4-[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methylthiazolidine-2,4-dione, potassium salt.

The data below shows the analytical data obtained for the three formulations during storage.

Months of storage	Formulation 1			Formulation 2			Formulation 3		
	Assay mg/tab	Degradation products		Assay mg/tab	Degradation products		Assay mg/tab	Degradation products	
		Largest single %	Sum %		Largest single %	Sum %		Largest single %	Sum %
0	9.73	0.20	0.63	8.83	0.22	0.70	9.11	0.23	0.77
1	-	-	-	6.02	4.02	8.78	8.28	2.44	7.05
3	9.27	3.67	4.83	7.99	6.02	13.83	8.25	3.94	10.99
6	8.79	1.51	4.37	NA	NA	NA	NA	NA	NA

As indicated, the stability of Formulation 1 is superior to that of Formulations 2 and 3, both of which contain "starch." Thus, for at least the reasons indicated above, Applicants respectfully submit that the references cited in the Office Action, even if combined, fail to disclose certain limitations of the present claims.

In any event, Applicants note that one of ordinary skill in the art would not have found it obvious to combine both Van Leverink and Staniforth et al. with Lohray et al. in the manner suggested in the Office Action. Staniforth et al., for instance, is directed to a method of preparing a solid dosage form by preparing an *aqueous slurry* that contains microcrystalline cellulose and an augmenting agent (e.g., silicon dioxide) and thereafter drying the slurry in a manner that exhibits quasi-hornification to obtain an agglomerated material. With respect to the process of forming the material, Staniforth et al. expressly states that "the particulate coprocessed product of this aspect of the present invention possesses desirable performance attributes that are *not present when the combination of microcrystalline cellulose and silicon dioxide are combined as a dry mixture*" (Column

8, lines 53-56 (emphasis added)). In stark contrast, Van Leverink teaches a process for producing anhydrous lactose by introducing "*dry product* into an extruder", (Column 2, Lines 10-13 (emphasis added)), through a process where "*water is not added*" (Column 2, Lines 65-66). Moreover, Van Leverink teaches it is known in the prior art that when anhydrous lactose is prepared in water-containing environments. This causes various problems ranging from unstable forms of anhydrous lactose to requiring additional drying steps which cause unacceptable hygroscopic properties. (Column 1, Lines 40-45; Column 2, Lines 62-64).

Thus, the teachings of Staniforth et al. and Van Leverink *expressly teach away from one another with respect to using dry and wet preparation processes*. Accordingly, one of ordinary skill in the art would not be induced to combine the references in the manner suggested in the Office Action. In fact, the only apparent incentive or motivation for using the teachings of these references in the manner suggested in the Office Action results from using Applicant's disclosure as a blueprint to reconstruct the claimed invention out of isolated teachings in the prior art, which is improper under *§ 103*.

Applicants emphasize that the differences between the present claims and the cited references are not simply a matter of obvious design choice. In fact, as previously emphasized in Applicants' responses, the use of low moisture content excipients, such as microcrystalline cellulose, results in a more stable composition. (Hjorth Declaration, 08/21/02). Even though such excipients may be generally known in the art, the cited references do not disclose the use of a low moisture content for decreasing the amount of degradation products present. Thus, for at least the reasons indicated, Applicants

respectfully submit that the present claims patentably define over the cited references, taken singularly or in any proper combination.

Applicants respectfully submit that the present application is in complete condition for allowance and favorable action, therefore, is respectfully requested. Examiner Kim is invited and encouraged to telephone the undersigned, however, should any issues remain after consideration of this Amendment.

Please charge any additional fees required by this Amendment to Deposit Account No. 04-1403.

Respectfully requested,

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